## REMARKS

Claims 1-7, 9-13, 15-20, 22-42 are pending in the present application. Claims 8, 14 and 21 were previously canceled without prejudice or disclaimer thereto. Claims 9-13 and 24-41 have been withdrawn from consideration as being drawn to non-elected subject matter.

In view of the following, further and favorable consideration is respectfully requested.

### 1. Rejection of claims 1-6, 15-16, 18-20, 22-23 and 42 under 35 U.S.C. §103(a)

The Official Action states that claims 1-6, 15-16, 18-20, 22-23, and 42 are rejected under 35 U.S.C. §103(a) as being unpatentable over Gilis *et al.* (WO 00/03697) and Ishibashi *et al.* (U.S. Patent Application No. 2003/0012815) in view of Lynenskjold *et al.* (U.S. Patent Application No. 2003/0211168) and Nara *et al.* (U.S. Patent No. 6,245,351).

As the basis for this rejection, the Official Action states in relevant part:

> Gilis *et al.* and Ishibashi *et al.* in view of Lynenskjold *et al.* and Nara *et al.* ...provide the teaching, suggestion and motivation to use any suitable solvent system in order to provide a working solution for coating core particles.

### Response

Applicant respectfully traverses this rejection of claims 1-6, 15-16, 18-20, 22-23, and 42. The cited references do not establish a *prima facie* case of obviousness against the presently pending claims.

To establish a prima facie case of obviousness, the PTO must satisfy three requirements. First, as the U.S. Supreme Court recently held in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (*KSR*, supra, slip opinion at 13-15). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.,* 18 USPQ 1016, 1023 (C.C.P.A 1970). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

## A. Presently claimed subject matter

The present pending claims as exemplified by currently pending independent claim 1 are directed to:

> A method of manufacturing a water-insoluble azole antifungal active agent oral dosage form, said method comprising the steps of: providing a single phase working solution comprising a water-insoluble azole antifungal active agent, water, a water-soluble polymer and a solvent, said solvent selected from the group consisting of alcohol, acetone, and mixtures thereof; providing core particles formed from a pharmaceutically acceptable material; combining said working solution with said particles to produce a water-insoluble azole antifungal active agent-coated particles; drying said water-insoluble azole antifungal active agent -coated particles; and forming said dried particles into an oral dosage form; wherein said working solution is essentially free of methylene chloride, and said oral dosage form is essentially free of methylene chloride.

## B. The Teachings of the Gilis *et al.* reference (WO 00/03697)

The Gilis *et al.* reference teaches pellets having a core coated with an antifungal and a polymer. The pharmaceutical dosage form disclosed in the Gilis *et al.* reference is prepared using a suitable solvent system comprising a mixture of dichloromethane and an alcohol. The Gilis *et al.* reference specifically teaches that the solvent mixture should comprise at least 50% by weight of dichloromethane (see p. 9, lines 17-20). Further, the Gilis *et al.* reference does not disclose a working solution containing both the drug and water, as required by the present claims.

## C. The Teachings of the Ishibashi *et al.* reference (U.S. Patent Application No. 2003/0012815)

The Ishibashi *et al.* reference discloses a sustained release formulation prepared by spray-coating a solution containing a hydrophobic organic substance-water-soluble

polymer mixture onto a drug-containing core substance, followed by spray-coating a different hydrophobic organic compound-water-soluble polymer mixture onto the resulting coating layer. The Ishibashi *et al.* reference teaches compositions formed by spraying a polymeric layer on top of a drug-containing core. This is different from the presently claimed process, which requires both the drug and the polymer in the same layer.

**D. The Teachings of the Lynenskjold *et al.* reference (U.S. Patent Application No. 2003/0211168)**

The Lynenskjold *et al.* reference teaches the production of spray-dried coated particles comprising an inert particulate carrier, a cellulosic binder, an active substance and water. Lynenskjold *et al.* teach the use of aqueous dispersions or solutions are preferred for the coating composition but alkanols (ethanol), ketones (acetone) and chlorinated hydrocarbons (methylene chloride) may also be used. None of the examples provided in the Lynenskjold *et al.* reference disclose the use of any of these solvents with water. This process of producing coated particles is different from the presently claimed process, which requires a water-insoluble azole antifungal, a water-soluble polymer, water and a solvent in the same working solution.

**E. The Teaching of the Nara *et al.* reference (U.S. Patent No. 6,245,351)**

The Nara *et al.* reference teaches a drug core coated with a composition comprising a water-insoluble substance, a swellable polymer and, optionally, a hydrophilic substance dissolved or dispersed in a solvent where the solvent can be water, an organic solvent or mixtures thereof. The organic solvent can be ethyl alcohol

or acetone. This is different from the presently claimed process, which requires both the drug and the polymer in the same layer.

**F. The combination of references does not show all the elements of the pending claims in one working solution, and thus cannot render these claims obvious**

The presently pending claims are distinguishable from the cited references. None of the references, taken alone or in combination, contain all the elements of the presently pending claims in the same working solution, and thus cannot render these claims obvious. In particular, independent claim 1 recites a single phase working solution comprising a water-insoluble azole antifungal active agent, water, a water-soluble polymer and a solvent, said solvent selected from the group consisting of alcohol, acetone and mixtures thereof, wherein said working solution is essentially free of methylene chloride, and said oral dosage form is essentially free of methylene chloride (Emphasis added).

In contrast, Gilis *et al.* and Ishibashi *et al.* both disclose dichloromethane as a suitable solvent. Accordingly, the solvent system recited in the present application is different from the solvent systems disclosed in the Gilis *et al.* and Ishibashi *et al.* references. The Gilis *et al.* reference does disclose that dichloromethane levels should be limited, however, the reference also teaches away from the present claims by including 50% dichloromethane in the solvent system. Nothing in the Gilis *et al.* reference suggests a solvent system that does not include dichloromethane. Further, the Gilis *et al.* reference teaches that azole antifungal compounds are sparingly soluble

in water, and that other non-aqueous based systems must be used in order to solubilize the compounds (see p. 1, lines 9-34).

The Ishibashi *et al.* reference teaches that solvents should be selected according to the hydrophobic organic compound and water soluble polymer used. However, the Ishibashi *et al.* reference discloses the use of dichloromethane and carbon tetrachloride as suitable solvents, which are specifically excluded from the presently pending claims. Further, the Ishibashi *et al.* reference does not state how to reduce or eliminate the levels of dichloromethane to the extent taught by the present application. Therefore, the Ishibashi *et al.* reference does not remedy the deficiencies of the Gilis *et al.* reference.

Regarding the Lynenskjold *et al.* reference, this reference teaches the production of spray-dried coated particles comprising an inert particulate carrier, a cellulosic binder, an active substance and water, while the presently pending independent claim 1 teaches a working solution comprising a water-insoluble azole antifungal active agent, water, a water soluble polymer and a solvent, said solvent selected from the group consisting of alcohol, acetone, and mixtures thereof. Lynenskjold *et al.* disclose that organic solvents can be used in the composition but an aqueous solution or dispersion is preferred. The organic solvent can be methylene chloride, ethanol or acetone. Lynenskjold *et al.* does not teach or suggest the combination of water and an organic solvent along with the water soluble polymer. The examples in the reference do not include organic solvents along with water in the production of the particulate compositions. Therefore, the Lynenskjold *et al.* reference does not remedy the deficiencies of Gilis *et al.* or Ishibashi *et al.* as it shows a different solvent system that

does not contain all the elements in the same working solution as required by the presently pending claims.

The Nara *et al.* reference teaches a drug core coated with a coating composition comprising a water-insoluble substance, a swellable polymer and, optionally, hydrophilic substances dissolved or dispersed in a solvent. While the solvents can be water, an organic solvent or mixtures thereof, this solvent system does not include a water-insoluble azole antifungal active agent or any other active agent. The presently pending claims require that the solvent system and the drug be in the same working solution and, in turn, be present in the same coating layer on the core particle. Therefore, Nara *et al.* does not remedy the deficiencies of Gilis *et al.* or Ishibashi *et al.* or Lynenskjold *et al.* as it does not show a coating solution that contains an active agent in the working solution as required by the presently pending claims.

None of the cited references disclose a working solution containing the drug, water-soluble polymer, solvent, and water, wherein the working solution is essentially free of methylene chloride as required by the present claims. Therefore, it would have been unexpected for a person having ordinary skill in the art to use water and an organic solvent to process a water-insoluble drug. Further, Ishibashi *et al.* and Nara *et al.* both teach compositions formed by spraying a polymeric layer on top of a core substance containing a drug. In contrast, the presently claimed process requires both the drug and the polymer to be contained in the same layer.

Accordingly, the Gilis *et al.*, Ishibashi *et al.,* Lynenskjold *et al.*, and Nara *et al.* references, taken alone or in combination, do not show all of the elements of the

presently pending claims in the same working solution, and thus cannot render these claims obvious.

## G. No motivation exists to combine the references and thus cannot render these claims obvious

The Examiner asserts in the Office Action that the applicant is attacking the references individually by pointing out how specific claim limitations are not met by the individual references. However, as noted in this response, the references, taken alone or in combination, do not teach each and every element of the presently claimed subject matter. In addition, the Examiner has established no motivation to combine the references.

With regard to motivation to combine references, **MPEP 2143** discusses the requirements of a *prima facie* case of obviousness. First, there must be some suggestion or motivation to combine the reference teachings or to modify the reference, and second, there must be a reasonable expectation of success. Finally, the prior art reference or references when properly combined must teach or suggest all the claim limitations.

Regarding motivation to modify properly combined references, **MPEP 2143.01** states that a proposed modification cannot render the prior art unsatisfactory for its intended purpose. If it does, then there is no suggestion or motivation to make the proposed modification. Further, the proposed modification cannot change the principle operation of a reference.

In *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.,* Federal Circuit, *No.* 06-1325 (June 28, 2007), the Federal Circuit rejected Alphapharm's argument that the prior art would have led one of ordinary skill in the art to select compound b as a lead compound most promising to modify in order to improve its antidiabetic activity and thus potentially arrive at the claimed pioglitazone. The Federal Circuit considered three references in reaching its determination, namely Takeda's '200 patent; Sodha II; and Takeda's '779 patent. The Federal Circuit found that Sodha II taught away from compound b and that any suggestion in the '779 patent to select compound b was essentially negated by the disclosure of Sodha II in view of the more exhaustive and reliable scientific analysis presented by Sodha II and the teaching away. Accordingly, the Federal Circuit accorded more weight to the Sodha II reference.

It is submitted that a *prima facie* case of obviousness has not been established because the Gilis *et al.*, Ishibashi *et al.*, Lynenskjold *et al.* and Nara *et al.* references fail to teach or suggest all of the limitations of the presently pending claims as required by *In re Wilson*. Further, a *prima facie* case of obviousness has not been established because the skilled artisan would have no motivation to modify Gilis *et al.* or Ishibashi *et al.* to incorporate the solvent system of Lynenskjold *et al.* or the solvent coating system of Nara *et al.*

Gilis *et al.* teaches a bead core coated with a very sparingly water-soluble drug and a hydrophilic polymer. The Ishibashi *et al.* reference teaches a drug core coated with a coating layer of a hydrophobic substance and a water-soluble polymer. Neither reference includes water in their respective coating layers. Lynenskjold *et al.* and Nara

*et al.* each teach a coating composition that contains water. One of ordinary skill in the art would not substitute the solvent system of Lynenskjold *et al.* or Nara *et al.* containing water with that of Gilis *et al.* or Ishibashi *et al.* Gilis *et al.* and Ishibashi *et al.* provide no motivation to provide water in their coating systems for a very sparingly soluble active agent and hydrophobic substance, respectively. Therefore, one of ordinary skill in the art would not look to Lynenskjold *et al.* or Nara *et al.* for a solvent system containing water to dissolve a very sparingly water-soluble active agent or a hydrophobic substance.

In further support of this argument, Applicants respectfully submit that the process of the presently pending claims provides particles that have an increased solubility under dissolution conditions at pH 5.0, resulting in enhanced bioavailability of the active ingredient. Table 5 on page 24 of the present specification shows that the azole antifungal composition had a dissolution rate increase by 129% over the dissolution profile of the commercial product SPORANOX® under fasted conditions. The table further shows that the dissolution rate increased by 74% over the commercial product under fed conditions.

In the final Official Action dated December 1, 2008, the Examiner found Applicants' unexpectedly superior results unpersuasive. In particular, the Examiner stated that "Applicants have not described exactly how the itraconazole particles tested in the example at page 24 were prepared (solvent system, water-soluble polymer, etc.) nor how the commercial SPORANOX® particles were prepared." In addition, the Examiner states that the itraconazole particles tested by Applicants are not

commensurate in scope with the patent protection being sought. *See* page 7 of the December 1, 2008 Official Action.

In response to the Examiner's comments regarding the unexpectedly superior results, Applicants direct the Examiner's attention to the parent application of the presently pending application, U.S. patent Application 09/933,032, U.S. Patent No. 6,663,897 (hereinafter "the '897 patent"), to provide the requested information regarding the process by which the itraconazole particles and SPORANOX® particles were produced. In addition, the '897 patent provides further dissolution test results to show the increased dissolution profile for the itraconazole particles of the presently pending application.

The itraconazole particulate compositions discussed in the present application are consistent with those described and disclosed at col. 6, line 1-67 of the specification of the '897 patent, as per the below listing. The below listing present in the '897 patent includes the percentages for each ingredient of the total composition and the specific quantity of each of the individual ingredients present therein.

Itraconazole and Hydrochloric Acid ratio is 1:1.6 Moles

| Name of Ingredient | Percent | Quantity |
|---|---|---|
| Microcrystalline Cellulose Spheres (Celpheres)[1] | 36.28 | 1,500 g |
| Micronized Itraconazole | 18.86 | 780 g |
| Hydroxy Propyl Methyl Cellulose 5 cps | 42.45 | 1,755 g |
| Titanium Dioxide USP | 0.85 | 35.1 g |
| Hydrochloric Acid 37% NF/EP[2] | 1.56 | 174.5 g |
| Alcohol SD3A Anhydrous[3] | 0.0 | 28,070 g |
| Purified Water USP/EP[3] | 0.0 | 3,264 g |
| Total | 100.0 | 4,134.66 g |

[1]CP 507 grade Celpheres ® are used
[2]Supplied as 37% Hydrochloric Acid and contributes 64.56 g of total solids
[3]Removed in the process

The itraconazole particulate composition was prepared according to the following steps:

a. A 19.22 kg portion of SD3A alcohol was added to a stainless steel container. The hydroxypropyl methyl cellulose was added under stirring. When it forms a uniform suspension, the purified water was added under stirring. The stirring was continued until a translucent solution was formed. At the end of stirring, titanium dioxide was added and stirring continued for another ten minutes until a uniform suspension was formed.

b. Next, a 6.85 kg portion of SD3A alcohol was combined with the hydrochloric acid and stirred for ten minutes. To this solution, the itraconazole was added under stirring and the stirring continued for an additional fifteen minutes.

c. Next, the itraconazole solution was added to the hydroxypropyl methyl cellulose solution under stirring and stirring continued for 20 minutes. After stirring was completed the solution was homogenized for 2 minutes. The pH of the solution is then checked and a 2.0 kg portion of SD3A alcohol

was added under impeller stirring. At this stage the weight of the solution is checked and adjusted accordingly with additional quantities of alcohol.

d. A Glatt GPCG-5 fluidized bed coater equipped with a Wurster spray insert is used for coating of the particles. Note that powder generation (spray drying) should be avoided and the filter bag placed properly to avoid losses. The spray rate is gradually increased from a starting rate of 15 grams to a final rate of 30 to 35 grams per minute towards the end of the process. Loading is performed at a temperature of 34-42° C. The coated particles are then dried for approximately 10-12 hours in a tray dryer at 45-50° C.

e. The coated particles described above are then used to fill a size 0, CAPSUGEL™ elongated hard gelatin capsule to provide a finished oral dosage having the ingredient weights and proportions as set forth below.

The SPORANOX® particles, which serve as the basis for comparison for the dissolution tests disclosed in the '897 patent, as well as the presently pending application, are available commercially. SPORANOX® is the subject of a New Drug Application (ND 20-083) which was approved on September 11, 1992 as a drug product. SPORANOX® is protected by U.S. Patent No. 5,633,015 (hereinafter "the '015 patent"). The '015 patent is assigned to Janssen Pharmaceutica N.V. The process by which the SPORANOX® particles are prepared is recited in an example of the '015 patent beginning at col. 4, line 63 and continuing through col. 6, line 15. The SPORANOX® particulate composition was prepared according to the following steps:

a) Itraconazole Spraying Solution

An inox vessel was charged with methylene chloride (375kg) and denatured ethanol (250 kg) through a filter *(5μ)*. Itraconazole (21.74 kg) and hydroxypropyl methylcellulose 2910 5 mPa.s (32.61 kg) was added while stirring. Stirring was continued until complete dissolution was obtained (A suitable saperconazole spraying solution was obtained using

an identical procedure).

b) Seal-Coating Spraying Solution

An inox vessel was charged with methylene chloride (21.13 kg) and polyethylene glycol 20000 (Macrogol 20000) (3.913 kg) while stirring. Denatured ethanol (14.09 kg) was added and the solution was stirred until homogeneous.

c) Drug Coating Process

A fluidized-bed granulator (Glatt, typeWSG 30) equipped with a 18 inch Wurster (bottom spray) insert was loaded with 25-30 mesh (600-700 μm) sugar spheres (41.74 kg). The spheres were warmed with dry air of 50°-55° C. The fluidizing air volume was controlled by opening the exhaust air valve to approximately 50% of its maximum in the beginning, increasing up to 60% at the end of the spraying process. The previously prepared itraconazole spraying solution was then sprayed on the spheres moving in the apparatus. The solution was sprayed at an initial delivery rate of about 600 to 700 $g.min^{-1}$ at an atomizing air pressure of about 3.5 $kg/cm^2$ (0.343 MPa). After delivery of about 30% of the spraying solution, the delivery rate was increased to 700-800 g/min.

When the spraying process was completed, the coated spheres were dried by further supplying dry air of 50°-55° C. for about 10 minutes. The coated spheres were then allowed to cool in the apparatus by supplying dry air of 20°-25° C. for about 10 to 20 minutes. The apparatus was emptied and the coated spheres were collected.

d) In-Between Drying

In order to minimize residual solvent levels the coated spheres were then subjected to a drying step. The coated spheres were introduced in a vacuum tumbler-drier and dried for at least 24 hours, preferably about 36 hours, at a temperature of about 80° C. at a pressure of about 200-300 mbar (20-30 kPa). The tumbler-drier was operated at its minimal rotation speed (2 to 3 rpm). The dried coated spheres were sieved with a sieve (Sweco S24C; sieve mesh width 1.14 mm).

e) Seal-Coating Process

The dried coated spheres were introduced again in the fluidized-bed granulator equipped with the Wurster insert and warmed with dry air of

50°-55° C. The previously prepared seal-coating spraying solution was then sprayed on the coated spheres moving in the apparatus. The solution was sprayed at an delivery rate of about 400 to 500 $g.min^{-1}$, at an atomizing air pressure of about 2.5 bar (0.25 MPa). When the spraying process was completed, the beads were dried by further supplying dry air of 50°-55° C. for 10 min. The coated spheres were then allowed to cool in the apparatus by supplying dry air of 20°-25° C. for about 5 to 15 minutes. The beads were removed from the apparatus and stored in suitable containers.

f) Capsule Filling

The drug coated beads were filled into hard-gelatin capsules (size 0) using standard automatic capsule filling machines (e.g. Model GPK.-1500, H60ffliger and Karg. 5 Germany). In order to obtain capsules with good weight distribution, capsule filling speed was reduced to about 75-85% of the maximum speed. Each capsule received approximately 460 mg beads, equivalent to about 100 mg itraconazole. Using the process parameters described above, itraconazole 100 mg hard-gelatin capsules were obtained which met all the requirements, in particular the dissolution specifications.

The itraconazole particles prepared by the process described in the '897 patent and described above, and the commercially available SPORANOX® particles were subjected to the same dissolution tests. The first dissolution test, conducted at a pH of 1.2, is described in Example 2 of the '897 patent at col. 7, line 1 through col. 8, line 40. The results of the dissolution test for each type of particles are set forth below.

Dissolution Test Results in Simulated Gastric Fluid (pH 1.2)

| Product Details | | Minimum | Maximum | Aver-age | Std. Dev. | % RSD |
|---|---|---|---|---|---|---|
| Example 1 Capsules | % Dissolved in 30 minutes | 83.3 | 91.0 | 87.0 | 3.7 | 4.3 |
| | % Dissolved in 60 minutes | 94.9 | 102.6 | 97.7 | 3.0 | 3.1 |
| | % Dissolved in 720 minutes | 102.0 | 103.1 | 102.7 | 0.5 | 0.5 |
| Sporanox Capsules | % Dissolved in 30 minutes | 47.7 | 79.2 | 59.4 | — | — |
| | % Dissolved in 60 minutes | 71.2 | 98.7 | 82.0 | — | — |
| | % Dissolved in 720 minutes | 86.4 | 102.8 | 96.6 | — | — |

The itraconazole particles prepared by the process described in the '897 patent and described above, and the commercially available SPORANOX® particles were also subjected to a second dissolution test, wherein the test was conducted at a pH of 5.0. This dissolution test is described in Example 3 of the '897 patent col. 8, line 41 though col. 9, line 18. The results of the dissolution test at a pH of 5.0 for each type of particles are set forth below.

Dissolution Data in pH 5.0 Phosphate Buffer.

| Product Details | | Minimum | Maximum | Aver-age | Std. Dev. | % RSD |
|---|---|---|---|---|---|---|
| Example 1 Capsules | % Dissolved in 30 minutes | 28.4 | 40.5 | 33.7 | 5.0 | 14.8 |
| | % Dissolved in 60 minutes | 56.1 | 64.1 | 61.0 | 3.6 | 5.9 |
| | % Dissolved in 720 minutes | 51.3 | 53.2 | 52.3 | 0.8 | 1.5 |
| Sporanox Capsules | % Dissolved in 30 minutes | 2.7 | 2.8 | 2.7 | — | — |
| | % Dissolved in 60 minutes | 5.7 | 6.8 | 6.3 | — | — |
| | % Dissolved in 720 minutes | 4.9 | 5.3 | 5.1 | — | — |

The dissolution tests at pH 1.2 and 5.0 referenced in the '897 patent, show that the water-insoluble azole antifungal particles prepared in Example 1 of the '897 patent display a significantly more rapid dissolution profile than the commercially available SPORANOX® particles. This finding indicates that the particles produced by the process of the presently pending application dissolve more rapidly than the SPORANOX® particles under pH conditions that represent both fed and fasted conditions in a subject receiving such treatment.

The increased dissolution profile of the particles produced by the process of the presently pending claims leads to an enhanced bioavailability of the active ingredient of the particles. This enhanced bioavailability is shown at Table 5 on page 24 of the presently pending application.

Further, the Supreme Court in *KSR* reiterated the framework for determining obviousness that was stated in *Graham v. John Deere Co.* 383 U.S. 1, 148 USPQ 459 (1966). The four factual inquiries that were recited in *Graham* are as follows: (1) Determining the scope and contents of the prior art; (2) Ascertaining the differences between the prior art and the claims in issue; (3) Resolving the level of ordinary skill in the pertinent art; and (4) Evaluating evidence of secondary considerations, such as unexpected results. Id. As stated in **MPEP 2141**, secondary considerations such as unexpected results must be considered in every case in which they are present.

Accordingly, if the Examiner insists on maintaining that a prima facie case of obviousness has been established against the presently pending claims, applicants respectfully submit that they have successfully rebutted this finding of obviousness by demonstrating unexpectedly superior results for the claimed subject matter. In this regard, applicants respectfully direct the Examiner's attention to Table 5 on page 24 of the presently pending application and the dissolution test results of the '897 patent, showing an unexpectedly superior dissolution profile over the commercial product. Accordingly, the presently claimed subject matter is not obvious in view of the references cited by the Examiner.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the current rejection to presently pending claims 1-6, 15, 16, 18-20, 22-23 and 42.

## 2. Rejection of claim 7 under 35 U.S.C. §103(a)

The Official Action states that claim 7 is rejected under 35 U.S.C. §103(a) as being unpatentable over Gilis *et al.* (WO 00/03697) and Ishibashi *et al.* (U.S. Patent Application No. 2003/0012815) in view of Lynenskjold *et al.* (U.S. Patent Application No. 2003/0211168) and Nara *et al.* (U.S. Patent No. 6,245,351) as applied to claims 1-6, 15-16, 18-20, 22-23, and 42 above, and further in view of Vladyka *et al.* (U.S. Patent No. 6,497,905).

As the basis for this rejection, the Official Action states in relevant part:

> Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to provide the claimed azole antifungal agent in the amorphous state because Vladyka *et al.* teach that these agents having low aqueous solubility will benefit from providing them in their amorphous state. The skilled artisan would reasonably expect that an azole antifungal agent in its amorphous state will exhibit increase solubility (Vladyka *et al.*, col. 5, lines 20-25) in the aqueous coating solutions as motivated and suggested by Gilis *et al.*, Ishibashi *et al.*, Lynenskjold *et al.*, and Nara *et al.* as discussed *supra*.

### Response

Applicant respectfully traverses this rejection of claim 7. The cited references do not establish a *prima facie* case of obviousness against the presently pending claims.

The teachings of Gilis *et al.*, Ishibashi *et al.*, Lynenskjold *et al.*, and Nara *et al.* are discussed above in Section 1, the contents of which are hereby incorporated by reference in their entirety. None of these references teach the active agent in an amorphous form.

The Vladyka *et al.* reference teaches a solid solution of an azole compound in an amorphous state dissolved in a molten solution of a hydrophobic vehicle, a stabilizing agent, a disintegrant and optionally a binder. This composition is formulated by melting the hydrophobic vehicle at a temperature above its melting point but below that of the azole compound and dissolving the azole compound in the hydrophobic vehicle, followed by a granulation and cooling step. In contrast, the presently pending claims require a working solution comprising a water-insoluble azole antifungal, a water-soluble polymer, water and a solvent that is coated onto a carrier particle. The process of the presently pending claims is completely different from the process taught by Vladyka *et al.* In addition, the process of Vladyka *et al.* is completely different from the references whose deficiencies it is meant to cure. None of the Gilis *et al.*, Ishibashi *et al.*, Lynenskjold *et al.*, and Nara *et al.* references teaches a melt granulation process to form a solid solution, as required by Vladyka *et al.*

Vladyka *et al.* does not cure the deficiencies of Gilis *et al.*, Ishibashi *et al.*, Lynenskjold *et al.*, and Nara *et al.* as it does not teach that an amorphous drug can be contained in a solution of water-soluble polymer, water and a solvent to be sprayed onto a core particle. In addition, there is no motivation to combine the teachings of Vladyka *et al.* with those of Gilis *et al.*, Ishibashi *et al.*, Lynenskjold *et al.*, and Nara *et al.* because one of ordinary skill in the art would not look to a reference teaching granulation of a melted solid solution to substitute components with a solution containing a water soluble polymer, water and a solvent to be coated onto a particle.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the current rejection to presently pending claim 7.

### 3. Rejection of claim 17 under 35 U.S.C. §103(a)

The Official Action states that claim 17 is rejected under 35 U.S.C. §103(a) as being unpatentable over Gilis *et al.* (WO 00/03697) and Ishibashi *et al.* (U.S. Patent Application No. 2003/0012815) in view of Lynenskjold *et al.* (U.S. Patent Application No. 2003/0211168) and Nara *et al.* (U.S. Patent No. 6,245,351) as applied to claims 1-6, 15-16, 18-20, 22-23, and 42 above, and further in view of Martindale: The Complete Drug Reference (Pharmaceutical Press, London, 2002, pages 1344-1349).

As the basis for this rejection, the Official Action states in relevant part:

> Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use any known surfactant, such as those taught by Martindale, in the manufacture of azole antifungal-coated particles. Gilis *et al.* teach that surfactants can be incorporated in pharmaceutical preparations comprising azole antifungal agents. As such, the skilled artisan would have been imbued with at least a reasonable expectation that the surfactants taught in Martindale would be amiable for use in coating methods suggested and motivated by the cited references.

**Response**

Applicant respectfully traverses this rejection of claim 17. The cited references do not establish a *prima facie* case of obviousness against the presently pending claims.

The teachings of Gilis *et al.*, Ishibashi *et al.*, Lynenskjold *et al.*, and Nara *et al.* are discussed above in Section 1, the contents of which are hereby incorporated by

reference in their entirety. None of these references teach the surfactants recited in Claim 17.

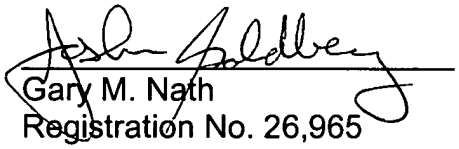
The Martindale reference is cited by the Examiner to show that various surfactants, some of which are recited in Claim 17, are suitable for use in pharmaceutical formulations. While the Martindale reference does recite surfactants that are suitable for use in pharmaceuticals, it fails to cure the other deficiencies of Gilis *et al.*, Ishibashi *et al.*, Lynenskjold *et al.*, and Nara *et al.* as none of the references alone or in combination teach a process of coating a core particle with a working solution of a water insoluble azole antifungal, a water soluble polymer, water and a solvent wherein the solvent is an alcohol, acetone or a mixture thereof.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the current rejection to presently pending claim 17.

## CONCLUSION

In view of the foregoing, applicants respectfully request the Examiner to withdraw the pending rejections and allow all pending claims 1-7, 15-20, 22-23 and 42 to proceed to grant. If the Examiner has any questions or wishes to discuss this matter, he is welcomed to telephone the undersigned attorney.

Respectfully submitted,
**THE NATH LAW GROUP**

By: 

Gary M. Nath
Registration No. 26,965
Joshua B. Goldberg
Registration No. 44,126
Customer No. 20529

Date: April 1, 2009
**THE NATH LAW GROUP**
112 South West Street
Alexandria, VA 22314
(703)-548-6284

GMN/JBG/RMJ:ROA.doc